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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/088,951	06/02/1998	MARTIN A CHEEVER	920010.535	2326

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/088,951	Applicant(s) Cheever et al
	Examiner Karen Canella	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 7, 9, 11, and 12* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 7, 9, 11, and 12* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *32*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

2. Claim 1 has been amended. Claims 1, 7, 9, 11 and 12 are pending and under consideration.

3. Claims 1, 7, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Disis et al (Journal of Immunology, 1996 May, Vol. 156, pp. 3151-3158) in view of Mamula et al (Journal of Immunology, 1994, vol. 152, pp. 1453-1461, reference AC of the I.D.S. submitted December 4, 2002) and any of Dyrberg and Oldstone, (in: Current topic in Microbiology and Immunology, 1989, Vol. 130, pp. 25-37), or Mamula et al (Journal of Immunology, 1992, Vol. 149, pp. 789-795) or Fedoseyeva et al (Transplantation, 1996, Vol. 61, pp. 679-683) or Mahi-Brown (Journal of Reproductive Immunology, 1992, Vol. 21, pp. 29-46).

Disis et al teach that overcoming tolerance to self-tumor antigens is key in the generation of effective anti-tumor immunity. Disis et al teach a method for overcoming self tolerance to the Her-2/neu antigen by the administration of sub-dominant epitopes of rat Her-2/neu. Disis et al further teaches that immunization with intact rat Her-2/neu failed to elicit rat neu specific responses. Disis et al do not teach immunization of rats with Her-2/neu of another species or immunization of humans with her-2 from another species as a method for overcome tolerance to Her-2/neu.

Mamaula et al (1994) teach a general model for eliciting T-cell immunity to self antigens (abstract, last sentence). Mamula et al teach that foreign proteins which have cross-reacting determinants generate auto-antigen presenting B cells which can activate an autoimmune T-cell response.

Dyrberg and Oldstone teach the concept of "molecular mimicry" wherein autoimmunity to a host self protein can be induced by homologous but non-identical epitopes produced by viral infections. Mamula et al (1992) teach a method to induce an immune response to self cytochrome

C in mice by immunizing with human cytochrome C or the immunodominant epitope of human cytochrome C consisting of residues 81-104. Fedoseyeva et al teach that transplantation of BALB/c mice (H2d) with splenocytes from allogenic BALB/c mice (H2a) resulted in the recognition of the immunodominant self peptide Dd as tolerance to said self peptide was broken by the presentation of the cross reactive peptide Kk. Ruoslahti et al teach that mice immunized with zona pellucida antigens from rat or pig developed an immune response against self zona pellucida as evidenced by disrupted follicular development. None of the references specifically teach an 80% amino acid identity to the self protein, but said level of identity would be inherent in the homologous proteins taught by the prior art.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to immunize humans with intact rat neu protein. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Disis et al on requirement for breaking self-tolerance to tumor antigens in order to elicit an effective anti-tumor immune response, the teachings of Mamula et al (1994) on the eliciting of an autoimmune t-cell response by the immunization of foreign cross-reacting determinants and on the further teachings of Dyrberg and Oldstone, Mamula et al, (1992) Fedoseyeva et al or Ruoslahti et al on the concept of overcoming self-tolerance by presenting to a host a homologous but non-identical protein.

4. Claims 1, 7-9, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Disis et al (Journal of Immunology, 1996 May, Vol. 156, pp. 3151-3158) and Mamula et al (Journal of Immunology, 1994, vol. 152, pp. 1453-1461, reference AC of the I.D.S. submitted December 4, 2002) and Dyrberg and Oldstone, (in: Current topic in Microbiology and Immunology, 1989, Vol. 130, pp. 25-37), and Mamula et al (Journal of Immunology, 1992, Vol. 149, pp. 789-795) and Fedoseyeva et al (Transplantation, 1996, Vol. 61, pp. 679-683) and Mahi-Brown (Journal of Reproductive Immunology, 1992, Vol. 21, pp. 29-46) as applied to claims 1, 7, 8, 11 and 12 above, and further in view of Spitler et al (US 5,925,362).

For the reasons stated above, the combination of Disis et al and Dyrberg and Oldstone, and Mamula et al and Fedoseyeva et al and Mahi-Brown render obvious the methods of claims 1, 7, 11 and 12. Neither Disis et al nor Dyrberg and Oldstone, nor Mamula et al nor Fedoseyeva et al nor Mahi-Brown teach an antigen associated with prostate cancer or PAP.

Spitler et al teach a method to elicit an immune response in humans by vaccination with human tumor antigens such as PSA, PAP, PMSA and adjuvant. Spitler et al teach that human PSA expressed recombinantly in insect cells result in post-translationally modified PSA which has different immunogenicity from PSA recombinantly expressed in human cells (column 5, lines 54-59). Spitler et al do not teach a method to elicit or enhance an immune response to by immunization with a xenogeneic protein homologous to PSA or PAP. However, for the specific reasons stated above, any of Dyrberg and Oldstone, Mamula et al, Fedoseyeva et al or Ruoslahti et al teach the concept of inducing immunity to self antigens in a host by presenting to said host a homologous but non-identical protein. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to elicit or enhance an immune response to human PSA or PAP by immunization with a xenogeneic protein homologous to PSA or PAP. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Dyrberg and Oldstone, Mamula et al, Fedoseyeva et al or Ruoslahti et al on the concept of inducing immunity to self antigens in a host by presenting to said host a homologous but non-identical protein. None of the references specifically teach an 80% amino acid identity to the self protein, but said level of identity would be inherent in the homologous proteins taught by the prior art.

5. Applicant argues that there is no motivation to combine Disis et al with Dyrberg and Oldstone, (in: Current topic in Microbiology and Immunology, 1989, Vol. 130, pp. 25-37), or Mamula et al (Journal of Immunology, 1992, Vol. 149, pp. 789-795) or Fedoseyeva et al (Transplantation, 1996, Vol. 61, pp. 679-683) or Mahi-Brown (Journal of Reproductive Immunology, 1992, Vol. 21, pp. 29-46) because Disis et al teaches different solution to overcoming tolerance to self tumor antigens. Applicant argues that it is not permissible to

combine the reference of Disis et al in a 103 rejection as Disis et al used peptide fragments of Her-2 neu to overcome the tolerance to the Her-2/neu antigen rather than intact Her-2/neu from a second species. This has been considered but not found persuasive. It is improper to combine references where the references teach away from their combination. In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir.1983). However, the fact that Disis et al used a different solution to overcome sel-tolerance not reliant upon use of the full length protein does not teach away from the claimed invention. Furthermore, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the references of Dyrberg and Oldstone, and Mamula et al and Fedoseyeva et al and Mahi-Brown all teach the administration of a homologous peptide obtained from a second species as a means to overcome self-tolerance in a first species. As these references teach a method for overcoming self-tolerance, it is appropriate to combine then with the Disis et al reference which teaches the need to over come self-tolerance.

Applicant further argues that Mamula et al (1994) taches away from the claimed invention as it is stated on page 1455 "B and T cell responses were quite distinct in their cross reactivity to foreign proteins, since the latter exhibited strict specificity for the foreign immunogen". This has been considered but not found persuasive. Mamula et al teaches that the cross reactivity to the foreign antigen is via B cells, however, Mamula et al also teaches that the generation of these cross reacting B cells activate autoimmune T-cells which results in a T-cell response to an autoantigen (for example figure 5 of Mamula et al). Thus, the end result of the process is the activation of a T-cell which will react with a self-antigen which is the same as that claimed.

6. Claims 1, 7, 8, 11 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Carson et al (US 5,679,647) as evidenced by Mamula et al (Journal of Immunology, 1994, vol. 152, pp. 1453-1461, reference AC of the I.D.S. submitted December 4, 2002).

Carson et al disclose a method of eliciting an immune response to a human self-tumor antigen comprising administering a polynucleotide which expresses a polypeptide from a non-human source, wherein said polypeptide mimics said human self-tumor antigen but is not identical to the human self-tumor antigen (column 27, lines 6-13, column 29, lines 56-64, claims 1 and 8). Carson et al further disclose organ-specific tumor associated antigens such as prostate-specific transmembrane protein (column 21, lines 42-61) as suitable targets for the disclosed method.

Mamaula et al (1994) disclose a general model for eliciting T-cell immunity to self antigens (abstract, last sentence). Mamula et al disclose that foreign proteins which have cross-reacting determinants generate auto-antigen presenting B cells which can activate an autoimmune T-cell response.

It is inherent in the method of Carson et al that the administered polynucleotides are expressed. Therefore the administration of polynucleotides equates with the administration of polypeptides. Further it is inherent that T-cell immunity will be elicited in the method of Carson et al as Mamula et al disclose the generation of an immune response against self antigens when a cross-reacting.

7. Claims 1, 7-9, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carson et al (US 5,679,647) as evidenced by Mamula et al (Journal of Immunology, 1994, vol. 152, pp. 1453-1461, reference AC of the I.D.S. submitted December 4, 2002) in view of Laus et al (US 6,080,409).

Carson et al do not teach prostatic acid phosphatase as a tumor associated antigen. Laus et al teach prostatic acid phosphatase as a tumor associated antigen.

Laus et al teach a method of stimulating an immune response comprising the administration of dendritic cells pulsed with peptides obtained from prostatic acid phosphatase (column 14, example 4).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the polynucleotide encoding prostatic acid phosphatase for the polynucleotide encoding prostate-specific transmembrane protein in the method taught by

Carson et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Laus et al on the efficacy of administering dendritic cells pulsed with peptides of prostatic acid phosphatase as a method of inducing cytotoxic T-cell response in vivo.

8. Applicant argues that Carson et al cannot be applied as a reference because Carson et al teaches the administration of polynucleotides versus polypeptides. This has been considered but not found persuasive. It is inherent in the method of Carson et al that the administered polynucleotides will be expressed as polypeptides, "In this embodiment it is believed that the APC take up the naked polynucleotide at or near the point of entry then carry them into lymphatic circulation. Once at a lymph node the APC will present the intra cellularly expressed protein as an antigen, thereby stimulating an immune response" (column 8, lines 1-5). Carson et al teach that where the antigen is a self antigen, modification of the polynucleotide to encode a self-antigen which mimics the self antigen is part of the claimed method (column 8, lines 41-45). Carson et al teach the method will induce CTLs without antibody formation (column 8, lines 60-62), thus fulfilling the specific embodiment of claim 1 with regard to a T-cell response.

9. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on December 4, 2002 prompted the new ground(s) of rejection presented in this Office action. Also, Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a) and MPEP § 609(B)(2)(i).. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
March 24, 2003

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